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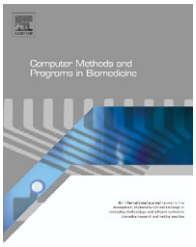

Describing the effectiveness of immunosuppression drugs and apheresis in the treatment of transplant patients

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ABSTRACT

When any foreign object is found in the human body antibodies are generated that mark it for removal by the immune system. In most cases these are natural and healthy responses; however, when considering organ transplants the immune response to the implanted organ must be kept to a minimum to avoid host rejection. To reduce the host's immune response to the implant, clinicians are able to manipulate the antibody dynamics through drug therapy, to minimise the antibody synthesis (immunosuppression), and by the removal of antibodies directly from the patients' blood, a process known as apheresis. In this paper models are presented that describe the *in vivo* kinetics of three immune complexes which are routinely measured pre- and post-operatively in implant patients, namely IgA, IgG and IgM. These models are then used to analyse the effective clearance rates of different apheresis methods (plasmapheresis, plasma absorption or plasma exchange) and to quantify the impact immune-suppression drugs have on the underlying antibody synthesis. It is hoped that the simplicity of the mathematical models, and associated implementation, will allow the translation of knowledge gained of the process dynamics to positively impact future patient diagnosis and treatment.

1. Introduction

Patients who receive a transplant normally incur an immune response to any implanted device or material. If left untreated this response can lead to damage of the implant and ultimately to rejection or failure, requiring it to be removed. To minimise rejection of the implanted organ or device clinicians have two treatment options: they can use drugs that restrict synthesis of antibodies (immunosuppression) and apheresis to clear antibodies directly from the blood [8].

There are several methods categorised under the term therapeutic apheresis; however, only three treatment types are used in this study: plasmapheresis (DFPP), plasma absorption (PA) or plasma exchange (PE). Plasmapheresis uses a centrifuge device that the blood is passed through to separate out molecules of a particular size, whilst proteins that are not to be removed are returned to the blood and re-introduced

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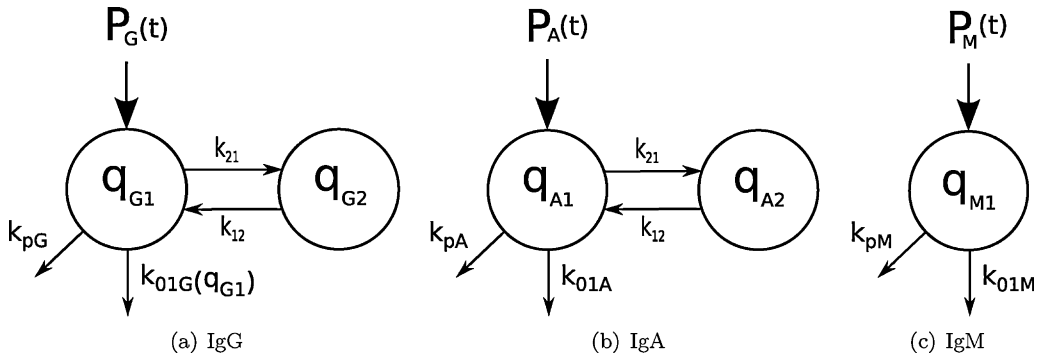

Fig. 1 – The three immunoglobulin models. The variables q_{Mi}, q_{Gi} and q_{Ai} denote the quantity of IgM, IgG and IgA in compartment i respectively; compartment 1 is plasma, 2 is EVF. k_{pM}, k_{pG} and k_{pA} are the effective apheresis clearance rates. k_{01^*} the natural clearance of the antibody.

into the patient's blood stream. Plasma absorption is a similar procedure but rather than a centrifuge a membrane that absorbs the relevant antibody is used. Plasma exchange is a simple process that involves removing a pre-defined volume of plasma over the treatment period, approximately 3 h, and replacing it with an equal quantity of a saline solution. This has the effect of removing a portion of the offending substance; however, it is a nonspecific treatment removing all substances from plasma, so unlike plasmapheresis and plasma absorption, which extract particular elements from plasma, plasma exchange is applied with strict limits, and is usually limited to three or four treatments over a two week period [3,4,8,20]. Both immunosuppression and apheresis can be conducted over a period of weeks before and after the surgery has been performed, thus requiring longitudinal data studies of the subjects. An understanding of the effectiveness of these treatments is vital for the early detection of transplant rejection, patient well-being and long term viability of the transplant.

There are several methods used to measure antibody concentrations (e.g. immunoelectrophoresis, immunoassay, immunofluorescence, immunoblot) [1,7]. A study of these measurement techniques is beyond the scope of this work. For this study, clinicians provided measurements of the antibody titres in standard units of concentration, generally g/L, and an estimate for measurement error [10].

The aim of this work is to enable clinicians to better categorise the patient's response to the implant, and observe the effectiveness of the treatment. Knowledge of these two facets will enable clinical staff to modify procedures earlier in a patient's treatment regime than was previously possible. For each patient it is common practice to measure three antibodies IgG, IgA and IgM to determine the immune response, each will be prevalent at different stages of the immune reaction. The current best practice to estimate treatment effect is to determine the response to the transplant through comparison of plasma concentrations; the results of such an analysis can be erroneous due to underlying process dynamics or interference from other treatments.

In this paper mathematical models are presented that allow the dynamics of the different apheresis modalities and immunosuppression treatments to be described. Analysis of these models with respect to the clinical data is then conducted, yielding a quantitative assessment of the treatment given to a range of kidney transplant patients, pre- and post-operatively.

2. Method

To investigate the *in vivo* kinetics of the immune complexes three models were constructed, one for each of the immunoglobulin types of interest: IgA, IgG and IgM. A compartmental schematic of each can be seen in Fig. 1. In the following sections each model will be described in more detail. In Fig. 1, the label $q_{*1}(t)$ indicates the quantity of the antibody present in plasma; whilst, $q_{*2}(t)$ is the quantity in extravascular fluid (EVF). $P_*(t)$ is the synthesis rate of the immunoglobulin, this is known to be non-constant over the period of observation due to the immune suppression and subsequent immune response to the transplanted kidney. All other rate constants are discussed in the relevant model section.

2.1. Natural clearance

Antibodies have a natural clearance mechanism to remove them from circulation within the body. For two of the antibodies (IgA and IgM) this has been found to be described adequately by a simple linear removal process [16], this is described in more detail in the sections below. However, antibody IgG has a more complex method of catabolism which requires further description.

It is known that clearance of the IgG protein is mediated through the FcRn receptor [2]. The rate of clearance is dependent upon the quantity of IgG in plasma due to binding and subsequent recycling via the epithelium. This is often referred to as the fractional clearance rate (FCR). If pseudo-steady state assumptions are made regarding the receptor dynamics the fractional clearance rate, $k_{01G}(\cdot)$, can be represented by [6,14,19]

$$k_{01G}(q_{G1}(t)) = \left(\alpha - \frac{V_m}{K_m + q_{G1}(t)}\right) \quad (1)$$